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10/001,725	10/22/2001	Kevin Pan	ORT-1517	7498

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EXAMINER
HUANG, EVELYN MEI

ART UNIT	PAPER NUMBER
1625	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/001,725	Applicant(s) PAN ET AL.	
	Examiner Evelyn Huang	Art Unit 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 10-18* is/are rejected.

7)☒ Claim(s) *5 and 7-9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. 1-5, 7-18 are pending. Claim 6 has been canceled according to the amendment filed on 7-1-2003.

Claim Rejections - 35 USC § 112

2. The 112 second paragraph rejection is withdrawn because the amendment has overcome the rejection.

Duplicate Claims

3. The objection to Claim 11 as being a substantial duplicate of claim 10 is maintained for reasons of record. Applicant maintains that claim 10 is drawn to a pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier while claim 11 is a product by process claim, drawn to a pharmaceutical composition made by mixing a compound of claim 1 and a pharmaceutically acceptable carrier. However, claim 11 has the same scope as claim 10, which although not specifically recited, has to be made by the process of mixing a compound of claim 1 and a pharmaceutically acceptable carrier as recited in claim 11. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 103

4. The rejection for Claims 1-4, 10-12 under 35 U.S.C. 103(a) as being unpatentable over Himmelsbach (5736559, PTO-1449) is maintained for reasons of record.

Applicant argues that only two of the 300 exemplified compounds are drawn to biphenyl containing a piperidinyl substituted with an aminocarbonyl or aminocarbonylalkyl, therefore Himmelsbach does not render the instant obvious.

On the contrary, Himmelsbach discloses a broad genus of compounds and describes a large number of diverse example compounds covering different aspects of the genus. Each example would represent a preferred genus. The cited Example 1 (6) on column 34 is within the most particularly preferred genus (column 5), and it differs from the instant in only one aspect, i.e. it has a methyl instead of the instant ethyl, propyl or benzyl on the amido nitrogen as R^1 and R^2. The instant compound is a homolog of Himmelsbach's example compound. To one of ordinary skill in the art, the homologs are expected to have similar activities. Furthermore, Himmelsbach, specifically teaches that methyl, ethyl, propyl, isopropyl and benzyl are optional choices within a small genus of compounds (column 2, line 33; lines 50-53). One of ordinary skill in the art would be motivated to replace Himmelsbach's methyl with the homologous ethyl, isopropyl or propyl, or the alternative benzyl to arrive at the instant invention with the reasonable expectation of obtaining an additional compound useful for inhibiting platelet aggregation since Himmelsbach had clearly taught that any species within the disclosed genus would be effective as anti-aggregation agent.

Applicant maintains that since Himmelsbach does not claim the 1-biphenyl-carbonyl, 4-aminocarbonyl- or 4-aminocarbonyl-substituted piperidinyl, it is not obvious to modify these compounds to arrive at the instant.

However, many reasons may account for these compounds not found in the claims. The absence of these compounds in the claims in this particular patent does not negate the positive teaching that they are among the most particularly preferred genus.

9. The rejection for Claims 1-3, 10-15 under 35 U.S.C. 103(a) as being unpatentable over Sugimoto (4895841) is maintained for reasons of record.

Applicant contends that only four of the 249 exemplified compounds of Sugimoto are drawn to a piperidinyl substituted with an aminocarbonylalkyl, and only one compound (Example 237 in column 107-108) contains two rings as in the instant. Therefore Sugimoto does not render the instant obvious.

On the contrary, Sugimoto discloses a broad genus of compounds and describes a large number of diverse example compounds covering different aspects of the genus. Each example therefore represents a preferred embodiment. The cited Example 49 on column 55-56 is within

the preferred genus and it differs from the instant in only one aspect, i.e. Sugimoto's example compound 49 does not have phenylmethyloxy on the phenyl as in the instant. However, Sugimoto teaches that the presence or absence of substituents on the phenyl is an optional choice (column 8, line 39 to column 9, line 1), an example of phenylmethoxy-substituted phenyl is shown on columns 107-108, Example 237. In view of Sugimoto's teaching, one of ordinary skill in the art would be motivated to replace Sugimoto's unsubstituted phenyl with the alternative, exemplified phenylmethoxy-phenyl to arrive at the instant invention with the reasonable expectation of obtaining an additional compound useful for inhibiting acetycholinesterase and thereby useful for treating CNS disorder such as dementia.

Claim Rejections - 35 USC § 112(1)

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 10-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification is only enabling for using the compounds of claims 5, 7-9 for treating emesis, pain depression or anxiety. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

a. *Nature of the invention.*

The instant invention is drawn to an amidoalkyl-piperidinyl compound for treating a nervous system disorder as recited on pages 20-21. The exact mechanism of the action of the inventive compound has not been determined, but may act by modulating the neurokinin receptor, including neurokinin-1, neurokinin-2 and neurokinin-3 receptors (page 11 of the specification).

b. *State of the prior art /level of the skill in the art.*

At present there is no known drug useful for treating any nervous system disorder, especially the various classes of nervous system disorders as described on pages 20-1, which are known to be of different origins and causes.

Since the disclosure suggests that neurokinin receptor may be involved in the instant, the following discussion is focused on neurokinin receptors antagonist to illustrate the state of the prior art and the unpredictability in the biological system.

Non-peptide neurokinin receptor antagonists have been described (Gao, Current Medicinal Chemistry, 1999, 6, 375-388). Although different diseases are implicated with the neurokinin receptors, the exact roles of neurokinin-1, neurokinin-2 and neurokinin-3 receptors have not been fully established (page 376).

The level of the skilled artisan in the neurokinin receptor art is high.

c) *The predictability/unpredictability of the art.*

The high degree of unpredictability is well-recognized in the neruokinin receptor art. A slight change in the structure of the compound would drastically change its biological activity and selectivity as evidenced in the different IC_{50} values for the various structurally similar neurokinin receptor antagonist compounds (page 381, Tables 3, 4; page 382, Tables 5, 6; page 383, Table 7; pages 385-6, Tables 8, 9).

d) *The amount of direction presented/working examples.*

Preparation of example compounds is limited to compounds wherein R4 is phenyl, pyridinyl, pyrrolidinyl, furyl, naphthyl, benzimidazolyl, imdiazolyl, tetrahydrofuryl, and R2 is CH_2-phenyl, phenyl, pyridinyl, pyrimidinyl, pyrrolidinyl or alkyl.

In vivo testing of DOI headshake model in mice is described in Example 13, the result shown for some of the compounds in Table 11. Reversal of Senkide-induced head shake in mice is described in Example 14. Results are shown for compounds 10, 15 in Table 12. Procedures for spontaneous locomotor activity test and elevated plus maze test are described in Example 15, the results shown for compounds 10, 15, 75. The procedure for anti-emetic test is described in Example 16, and compound 10 is recited to be active in the test.

e) *The breadth of the claims.*

Applicant's assertion that all the instantly claimed compounds with structures far removed from the example compounds would be effective in treating any nervous system

disorder as recited on pages 20-21, do not commensurate with the scope of the objective enablement, especially in view of the high degree of unpredictability and the limited working examples (paragraphs b) to d) above). There is no basis for one of ordinary skill in the art to extrapolate the results of the working examples in the above paragraph to treatment of nervous system disorder of diverse origins and causes, such as eating disorders, cerebrovascular diseases, neurodegenerative disorders, Alzheimer's disease etc, etc., especially when the mechanism of action of the inventive compound has not been determined.

f) *Quantitation of experimentation necessary.*

Since insufficient teaching and guidance have been provided in the specification (paragraphs b) to f) above), one of ordinary skill in the art, even with high level of skill, would not be able to use all the compounds as claimed without undue experimentation.

Allowable Subject Matter

11. Claims 5, 7-9 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The instant compound differs from Himmelsbach's compound (see paragraph 8 above) in having a different R2 and R4. Motivation to modify Himmelsbach's compound via multiple changes to arrive at the instant invention is lacking.

The instant compound differs from Sugimoto's compound (see paragraph 9 above) in having a different $L^{2.}$ Motivation to modify Sugimoto's compound to arrive at the instant invention is lacking.

The method of using the inventive compound to treat depression and anxiety is not taught or suggested by Himmelsbach or Sugimoto.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 703-305-7247. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Alan Rotman can be reached on 703-308-4698. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Evelyn Huang
Primary Examiner
Art Unit 1625

September 17, 2003